Evolution of Diversity and Complexity by Cryptic Variations in Gene Regulatory Networks

博士論文（要約）

Evolution of Diversity and Complexity by Cryptic Variations in Gene Regulatory Networks

(遺伝子制御ネットワークの隠蔽変異による多様性と複雑性の進化)

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Organisms have various forms and life-styles, which surprise me with their diversity and complexity. The traits, without exception, have been developed in the history of evolution with their roots in a simple common ancestor. This fact makes me conscious of some mechanistic principles behind the diversification and complexification of life. My major goal as an theoretical biologist is to formulate this stochastic process. This attempt will be a critical step toward a comprehensive understanding of "Tree of Life". I have been working on the problem focusing on the two properties combined in gene regulatory networks (GRNs)—robustness and evolvability.

Driving force of evolution is genetic variation, the quantity of which in a population determines the speed and direction of phenotypic evolution (Hansen and Houle 2008; Lande 1976; Lande and Arnold 1983). While adaptive phenotypic evolution depends on heritable variation in phenotypes, selection on phenotypes exhausts genetic variance, resulting in a limit to the selection response (Blows and Hoffmann 2005; Blows 2007). The maintenance of genetic variation has therefore been a major concern in evolutionary biology. Furthermore, concerted action of multiple genetic modifications are often necessary for organisms to produce a new complex traits (Monteiro and Nogueira 2010; Muller and Newman 2005). It is a long-disputed question how organisms could go through useless or deleterious intermediate stages, fitness valleys (Masel 2006; Stern 2011).

A group of organisms exhibit larger phenotypic variance when they encounter a novel environment than they usually do (Schlichting 2008; Takahashi 2013). It indicates the existence of invisible variations, i.e., cryptic genetic variations (CGVs), which would emerge as diverse phenotypes in response to the changes in environmental or genetic background. Such mechanisms that enable accumulation and release of CGVs are called evolutionary capacitor and considered to contribute to macro-evolutionary patterns such as saltatory evolution and adaptation to novel environments (Gibson and Dworkin 2004; McGuigan and Sgro 2009; Rutherford and Lindquist 1998; Schlichting 2008; Wagner 2005).

However, it is not always possible for organisms to produce any desired traits with recurrent mutations; although mutations occur at random positions in a genome, their effects are not random nor additive, but are constrained and biased by their developmental pathways (Pigliucci and Preston 2004; Smith et al. 1985; Wagner and Altenberg 1996; Wilkins 2007). Therefore, assuming the simple allelic effects on phenotypes is insufficient to understand the

evolution of phenotypic novelty; instead, considering how genetic variations are translated into phenotypic variations is necessary. A novel phenotype is not necessarily the product of a novel gene, but rather often emerges when a novel expression pattern is created with existing genes (Prud'homme et al. 2007; Shubin et al. 1997, 2009). Gene regulatory network (GRN) is in this sense the key stone of evolutionary novelty. GRNs control the spatial and temporal patterns of gene expression and are ubiquitously involved in biological processes such as cell differentiation, environmental responses, pattern formation and circadian rhythm (Davidson 2006; Evans and Marcus 2006; Farkas et al. 2006). Modularity of GRN enables co-option of a existing functional unit for another context and provide the useful material for phenotypic novelty (Carroll et al. 2004; Fraser et al. 2009; Masel and Trotter 2010; Monteiro 2012; Wilkins 2007).

Also GRNs are considered to be a candidate of evolutionary capacitor because of their epistatic behavior and mutational robustness (Siegal and Bergman 2002; Wagner 1996); thus GRNs can facilitate macro-evolution not only by modularity, but also through cryptic variations. However, the nature of cryptic variations in GRNs is poorly understood because most studies on the evolvability of GRNs hardly paid careful attention to population dynamics (Aldana et al. 2007; Ciliberti et al. 2007; Draghi and Whitlock 2012; Espinosa-Soto et al. 2011; von Dassow et al. 2000). CGVs should be accumulated through population genetic processes, such as mutations, genetic drift, and natural selection. It is therefore essential to understand how GRNs are modified in evolutionary processes under various conditions and how they can contribute to the phenotypic evolution through cryptic variations.

Here I constructed an individual-based model of GRNs that controlled gene expression in response to environmental stimuli. The model enabled the analysis of network properties in the context of population genetics. It demonstrated that populations of GRNs accumulate and release cryptic variations, the number of which varies depending on the properties of the GRNs and the environments to which they have been subjected across the generations. Large and complex GRNs are preferentially evolved under heterogeneous and fluctuating environment; such GRNs tend to exhibit higher potential for accumulation and release of CGVs and thus for new adaptation. These findings indicate that the expansion of GRNs and adaptation to novel environments are mutually facilitating, resulting in a sustainable sources of evolvability. This study thus provides important insight into the origins of biological diversity and complexity. The

progress in genome decoding techniques will soon enable the analyses of GRN structure within and among populations. For the future, this study provides the theoretical framework to understand how GRN structure and cryptic variations in a population will behave on an evolutionary timescale.

An important factor I ignored in this thesis is stochastic noise in gene expression. The expression of duplicated genes was more diverse than that of singletons (Dong et al. 2011; Ha et al. 2009; Kliebenstein 2008); individuals with larger GRNs genes may have advantages in diverse environments because they produce more genetically variable offspring. Therefore, considering stochastic effects of gene duplication may expand the parameter range in which environmental fluctuations facilitate the GRN evolvability.

Stochastic noise has importance aside of that aspect; it may facilitate GRN evolution and phenotypic novelty especially in unicellular organisms through the intermediate state called phenotypic accommodation (West-Eberhard 2003), partial penetrance (Eldar et al. 2009) or persistence (Wakamoto et al. 2013). Whereas deterministic dynamics is dominant when the cellular activity is high, stochastic fluctuation overwhelms deterministic component of the dynamics when the cellular activity is low under stressful environments (Kashiwagi et al. 2006). Then cells can find the new optimal phenotypes in stressful environments without guided by programmed pathway to express them. Genetic basis that more stably express such novel phenotypes that originally produced with stochasticity or plasticity can evolve and be fixed afterward (phenotypic assimilation; West-Eberhard 2003). I think it will be a major route for a horizontally transferred free gene to be integrated as a terminal node of GRNs, and that is why genes derived from horizontal transfer are abundant in terminal genes, not transcription factors (Lagomarsino et al. 2007).

This scenario can be extended to multicellular organisms, which have capacity to produce functional outcomes despite physiological, developmental, environmental change. A striking example is the evolution of tetrapod forelimb to a bird or bat wing. It needs concerted changes in bones, muscles, nerves, and vessels, but co-evolution of all these tissues with many regulatory changes in parallel is not necessary. Each component are developed through interactions with each other called exploratory processes (Kirschner et al. 2005) or self-organization (Kauffman 1993). Complex phenotypic changes can be produced with a small

number of genetic modification in this way. Such "facilitated variations" will be a key player that literally facilitate the evolution of complex traits (Gerhart and Kirschner 2007).

A theory of macro-evolutionary dynamics should fulfill two requirements. First, the potential of "facilitated variations" has to be quantified. A possible solution today is to measure the degree of phenotypic integration (Pigliucci and Preston 2004) by morphometrics, or some statistics on modularity of a GRN may be good proxies for that. The effect of facilitation can be examined by phylogenetic analysis. Second, the model must be designed from the viewpoint that individual GRNs constitute their own environment and thus ecosystem; niche construction should be included in phenotypes, and phenotypes should affect the evolutionary trajectories of other genotypes. It can be considered as a kind of game theory, but is different in that a new theory aims not at reaching an optimum nor equilibrium, but at divergence toward diversification and complexification. Modeling the interplay between ecology and development in this manner will lead us to a comprehensive understanding of macro-evolutionary pattern.